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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,699	08/05/2003	Pablo Umana	1975.0010004/TJS	5489

26111 7590 10/31/2006

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EXAMINER	
BURKHART, MICHAEL D	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 10/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/633,699	UMANA ET AL.	
	Examiner	Art Unit	
	Michael D. Burkhart	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/24/2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *109-142* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *109-142* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/24/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt and entry of the amendment dated 7/24/2006 is acknowledged. After entry of the amendment, claims 109-142 are pending and under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 109-142 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **These are new grounds of rejection.**

Claims 109, 110, 118 (from which all other claims depend) recite a glycoengineered antibody with an increased proportion of nonfucosylated oligosaccharides (or GlcNAc residues in claim 118) compared to "the corresponding antibody produced by the same host cell that has not been glycoengineered." There is no mention of a glycoengineered host cell in any of the claims, only a glycoengineered antibody. Thus, the claims lack antecedent basis for the term "the same host cell that has not been glycoengineered." Furthermore, this discrepancy makes it unclear what is to be glycoengineered in the claims, the host cell or the antibody. Antibodies can be glycoengineered (by use of glycosidase inhibitors or expression in different cell lines) without the use of a genetically glycoengineered host cell. The skilled artisan could not determine if such antibodies would infringe on the claimed antibodies because there is no clear basis for comparison. Thus, the metes and bounds of the claimed subject matter are unclear. This rejection affects dependent claims 111-117, 119-123, and 125-142.

Claims 109, 110, 118 recite the limitation "the corresponding antibody" in line 5. There is insufficient antecedent basis for this limitation in the claim. It would be remedial to recite "a corresponding antibody." This rejection affects all dependent claims.

Claim 111 recites the limitation "the predominant N-linked oligosaccharide"" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 116 recites the limitation "the predominant N-linked oligosaccharide"" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 117 recites the limitation "the corresponding antibody " in line 4. There is insufficient antecedent basis for this limitation in the claim. It would be remedial to recite "a corresponding antibody."

Claim 118 recites an antibody that has an increased proportion of GlcNAc residues "relative to the proportion of fucose residues compared to the corresponding antibody." What is being compared to what? The claim recites two different proportions and only one basis for comparison. Is the fucose proportion greater or less than relative to the corresponding antibody? Is the GlcNAc proportion increased relative to the corresponding antibody, or are both the GlcNAc and fucose proportions increased? Is the GlcNAc proportion greater than the number of fucose residues when compared to a corresponding antibody? It cannot be determined from the claims what exactly the glycan content of the claimed antibodies must be. Hence, the metes and bounds of the claimed subject matter are unclear. This rejection affects all dependent claims.

Claims 130-132 recite the limitation "the majority of the N-linked oligosaccharides" in line 2. There is insufficient antecedent basis for this limitation in the claim. It would be remedial to recite "a majority of the N-linked oligosaccharides."

Claim 134 recites the limitation "the majority of oligosaccharides" in line 4. There is insufficient antecedent basis for this limitation in the claim. It would be remedial to recite "a majority of oligosaccharides." This rejection affects all dependent claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 109-142 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection. This is a New Matter rejection.**

Applicants claim recombinant antibodies having increased Fc-mediated cellular cytotoxicity (ADCC) wherein said antibodies have an increased proportion of nonfucosylated N-linked oligosaccharides (all of the pending claims), or further comprise an increased proportion GlcNAc residues (pending claim 117), or have an increased proportion of GlcNAc residues relative to the proportion of fucose residues (pending claims 118-121), or wherein the predominant N-linked oligosaccharide is not a high mannose structure (pending claim 116). The first disclosure of such broad limitations was in claims 106 and 107 (now canceled) of the preliminary amendment of 12/22/2004. No such limitations are found in the claims as originally filed in this application (10/633,699, claims 1-85, filed 8/5/2003). There is no support for such broad limitations, or evidence that applicants considered such limitations as a part of their

invention, in the parent application, 09/294,584 (now U.S. patent 6,602,084), thus the instant claims comprise New Matter. Rather, applicants' disclosure repeatedly indicates that antibodies engineered to have an increased proportion of complex N-linked oligosaccharides with bisecting GlcNAc (e.g. column 6, lines 26-28 and lines 46-53, column 7, lines 14-26 and column 16, lines 55-61 of the '084 patent) are the invention. Non-fucosylated oligosaccharides are only mentioned in reference to a single example of a specific antibody produced in modified CHO cells, (i.e. the CE7-15t, -30t, and -60t preparations from Example 3, column 26 of the '084 patent) and are not disclosed as correlated with an increase in ADCC for this antibody, or for antibodies in general. Rather, the increase in ADCC for the CE7 antibodies was correlated with an increase in bisected complex oligosaccharides (column 27, lines 9-13), not a decrease in fucosylated oligosaccharides. This is probably because the sample with the greatest proportion of non-fucosylated oligosaccharides, CE7-15t, did not show an increase in ADCC (see Figs. 9 and 12 of the '084 patent). Hence, the instant claims are given a priority date of 8/5/2003, the filing date of the instant application. It is noted that applicants do have inherent support for antibodies claimed in a proper product-by-process format, wherein the method steps are based on the cells and enzyme used in Example 3. If applicants choose to so amend the claims, applicants are advised to ensure the instant application is in accordance with the requirements for the deposit of biological materials under the Budapest Treaty (e.g. for the CHO-tet-GnTIII cell line used in Example 3).

Claim Rejections - 35 USC § 102

The instant claims are product by process claims, and thus the claimed product is not limited by the recited method steps, only the structure implied by the steps. See MPEP §2113. For reasons set forth below, and absent evidence to the contrary, the prior art antibodies cited below have all of the claimed structural and functional limitations. **The following are new rejections.**

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 109, 110, 114, 117, 122-124, 131, 133, 135, 136, and 140-142 are rejected under 35 U.S.C. 102(b) as being anticipated by Kilmartin et al (J. Cell Biol., 1982) as evidenced by Shinkawa et al (JBC, 2003).

Kilmartin et al teach a rat antitubulin monoclonal antibody produced in YB2/0 cells (see abstract and pages 577-579) that inherently has a greater proportion of nonfucosylated residues than the same antibody produced in other cell lines. As evidenced by Shinkawa et al, the YB2/0 cells express low levels of α1,6-fucosyltransferase, therefore producing antibodies having a greater proportion of nonfucosylated oligosaccharides than those produced in CHO cells. For example, YB2/0-produced antibodies had 34% and 91% nonfucosylated oligosaccharides versus 9% nonfucosylated oligosaccharides for antibodies produced in CHO cells (see entire document, in particular Fig. 2, Table I, and page 3469, first column, last ¶). Furthermore, the low levels of fucosylated oligosaccharides were linked to an increase in ADCC (see abstract Figs. 1, 3, and 4,

and page 3469, second column to page 3470, first column), which was attributed to an increase in affinity for FcγRIII receptor (page 3466, second column, fourth ¶). The YB2/0 cells also had an increased content of GlcNAc than the CHO-produced antibodies (page 3469, first column, second ¶).

Thus, the functional limitations of the claimed antibodies, and the glycan structure, were inherent properties of the antibody taught by Kilmartin et al.

Claims 109-111, 114, 122-128, 131, 133, 135-136, 138, and 140-142 are rejected under 35 U.S.C. 102(b) as being anticipated by Rothman et al (Mol. Immunol, 1989, cited by applicants) as evidenced by Shields et al (JBC, 2002) and Wright et al (TIBTECH, 1997, cited by applicants).

Rothman et al teach the production of murine anti-tumor monoclonal antibodies (MAbs) in cells treated with a series of carbohydrate processing inhibitors such as Castanospermine (Cs), N-methyldeoxy-nojirimycin (MdNM), deoxymannojirimycin (DMM), monensin (Mon), and swainsonine (Sw), see entire document, particularly the abstract and page 1114, first column, second full ¶. One such antibody, CO-17-1A, is directed to an antibody expressed on a human colon cancer cell line (page 1114, second column, third full ¶). Treatment with Cs, Mon, and DMM increased the ADCC activity of the MAbs (Figs. 5 and 8), which was dependent upon interaction with the Fc receptor (Fig. 6). The increase in ADCC was at the least 80% compared to the "native" IgG (Fig. 5). The modified oligosaccharides of the MAbs were characterized as lacking fucosylation (page 1122, first column, first full ¶) which was correlated with enhanced ADCC (*ibid*, third full ¶). As evidenced by Wright et al, treatment with Cs or DMM inhibits an

early step in the glycan processing pathway, resulting in high mannose structures without fucose (see Fig. 2, structure 1 and page 29, second column). As evidenced by Shields et al, lack of fucose on the antibody oligosaccharides increases affinity for the FcγRIII receptor (see entire document, particularly the title and abstract). Thus, the functional limitations of the claimed antibodies, and the glycan structure, were inherent properties of the antibodies taught by Rothman et al.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 109, 110, 120, and 133 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 113-116 and 256-258 of copending Application No. 10/981,738.

Claims 109, 110, 114, 115, and 133 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 96-98, 108-111, 213, 261-263, and 273-276 and 256-258 of copending Application No. 10/761,435.

Claims 109, 114, 115, 128, and 133 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 74-85 of copending Application No. 10/633, 697.

Claims 109 and 133 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 127 of copending Application No. 10/437,388. **The above rejections are maintained for reasons made of record in the previous Office Action and for reasons set forth below.**

Response to Arguments

Applicant's arguments filed 7/24/2006 have been fully considered but they are not persuasive. Applicants indicate terminal disclaimers will be filed upon indication of allowable subject matter. However, since no terminal disclaimer has been filed, the rejections are maintained.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael D. Burkhart whose telephone number is (571) 272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael D. Burkhart
Examiner
Art Unit 1633

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER